

Table S1: Abbreviations, Terms, and Symbols

Abbreviation	Definition
AGEIND	age indicator variable which takes the value of 0 at age 40 or under and a value of 1 at ages above 40
AIC	Akaike's information criterion
BSA	body surface area calculated using the method of Mosteller
BSV	between subject variability
CKDEPI	Chronic Kidney Disease Epidemiology Collaboration equation
CL	clearance
COV	covariate
COVAR	covariance step
CV	coefficient of variation
DF	degrees of freedom
EGFR	estimated glomerular filtration rate calculated using the CKDEPI equation and expressed in absolute units (mL/min).
EGFR_BSA	estimated glomerular filtration rate calculated using the CKDEPI equation and normalized to standard BSA (mL/min/1.73 m ²).
HGB	hemoglobin
HT	height
ICU	intensive care unit
IWRES	individual weighted residual
KA	absorption rate constant
LOESS	local polynomial regression
MIN	minimization of the objective function value
OFV	objective function value (-2 log likelihood)
PAR	parameter
PLT	platelets
REF	reference model
ROUND	rounding errors
RV	residual variability
SCR	serum creatinine
SD	standard deviation
TVCL	typical value of clearance for the population
TVCLNR	typical value of non-renal clearance for the population
TVCLR	typical value of renal clearance for the population
TVKA	typical value of the absorption rate constant
TVV	typical value of volume for the population
V	volume of the central compartment
WT	weight

Table S2: Demographic and Clinical Characteristics of Patients Included in Toxicity Analysis

	All Patients N = 341	eGFR < 60 mL/min/1.73 m ² N = 133 (39.0%)	eGFR ≥ 60 mL/min/1.73 m ² N = 208 (61.0%)	P-value
Demographics				
Age (years)	54 (17)	59 (15)	50 (17)	<0.001
Sex				
Male	199 (58.4%)	79 (59.4%)	120 (57.7%)	0.84
Female	142 (41.6%)	54 (40.6%)	88 (42.3%)	
Race				
Black	39 (11.4%)	16 (12.0%)	23 (11.1%)	0.51
Caucasian	280 (82.1%)	106 (79.7%)	174 (83.7%)	
Other	22 (6.5%)	11 (8.3%)	11 (5.3%)	
Height (cm)	170.9 (11.2)	171.2 (12.0)	170.7 (10.7)	0.69
Weight (kg)	88.0 (31.4)	94.1 (31.9)	84.1 (30.4)	0.004
Clinical Baseline				
Charlson index	4 (2,7)	5 (3,7)	3 (1,7)	0.001
Total bilirubin (mg/dL)	0.81 (0.99)	1.02 (1.21)	0.67 (0.79)	0.001
Hemoglobin (g/dL)	9.4 (1.9)	9.0 (1.7)	9.6 (1.9)	0.004
Platelets (x 10 ³ cells/µL)	279.5 (151.8)	230.7 (109.2)	310.6 (166.6)	<0.001
SCR (mg/dL)	1.46 (1.43)	2.60 (1.74)	0.72 (0.27)	<0.001
EGFR (mL/min/1.73 m ²)	77.6 (43.2)	32.8 (15.6)	106.2 (28.0)	<0.001

Data presented as n (%), mean (standard deviation), or median (lower quartile, upper quartile).

P-value represents comparison between the two eGFR groups

Table S3: Base Model Parameter Estimates

Parameter	Estimate	Relative Standard Error (%)	Shrinkage
Fixed Effects			
TVCL (θ_1) [L/hr]	4.71	3%	
TVV (θ_2) [L]	48.20	4%	
TVKA (θ_3) [hr ⁻¹]	1.22	23%	
Between-subject Variability (BSV)^a			
BSV CL (ω_1) [%CV]	67.8%	4%	13%
BSV V (ω_2) [%CV]	30.5%	28%	28%
Correlation BSV CL-V ^b	0.857	--	
Residual Variability (RV)			
Additive Error (θ_4) [mg/L]	1.58	15%	
Proportional Error (θ_5) [%CV]	26.8%	6%	

^a BSV calculated as $\sqrt{e^{\omega^2} - 1}$

^b Expressed as correlation coefficient (r)

Table S4: Forward Selection of Covariates

PAR	COV	Functional Form	DF	MIN, ROUND, & COVAR Successful	OFV (Δ OFV)	AIC (Δ AIC)	BSV CL	BSV V
Round 1 (Reference Model: Base)								
REF	--	--	--	--	5362.046	5378.046	67.8%	30.5%
CL	WT	Linear	1	YES	5334.597 (-27.45)	--	63.4%	29.3%
CL	WT	Allometric	0	YES	5338.641 (-23.40)	--	62.7%	28.6%
CL	WT	Power	1	YES	5333.899 (-28.15)	--	63.4%	29.3%
CL	WT	Exponent	1	YES	5335.800 (-26.25)	--	63.5%	29.4%
CL	HT	Linear	1	YES	5330.843 (-21.20)	--	64.0%	30.0%
CL	HT	Power	1	YES	5329.616 (-32.43)	--	63.7%	29.9%
CL	HT	Exponent	1	YES	5329.294 (-32.75)	--	63.6%	29.9%
CL	BSA	Linear	1	YES	5327.104 (-34.94)	--	62.5%	29.2%
CL	BSA	Power	1	YES	5327.160 (-34.89)	--	62.5%	29.2%
CL	BSA	Exponent	1	YES	5328.325 (-33.72)	--	62.5%	29.2%
CL	AGE	Linear	1	YES	2309.353 (-52.69)	--	64.4%	31.6%
CL	AGE	Piecewise	1	YES	5299.85 (-62.19)	--	64.0%	31.6%
CL	AGE	Power	1	YES	5326.047 (-36.00)	--	65.5%	31.5%
CL	AGE	Exponent	1	YES	5314.430 (-47.62)	--	64.7%	31.5%
CL	SEX	Add Shift	1	YES	5354.442 (-7.60)	--	66.7%	30.4%
CL	ICU	Add Shift	1	YES	5360.594 (-1.45)	--	67.6%	30.7%
CL	SCR	Linear	2	YES	5310.127 (-51.92)	--	68.3%	32.2%
CL	SCR	Power	2	YES	5282.653 (-79.39)	--	65.4%	32.4%
CL	SCR	Exponent	2	YES	5285.17 (-76.88)	--	64.8%	32.3%
CL	EGFR	Linear	2	YES	5229.671 (-132.37)	--	59.8%	32.6%

CL	EGFR	Power	2	YES	5226.141 (-135.90)	--	59.3%	32.2%
CL	EGFR	Exponent	2	NO	--	--	--	--
CL	EGFR	Hill	4 ^a	YES	5225.102 (-136.94)	5247.102 (-130.94)	58.7%	31.8%
CL	EGFR BSA	Linear	2	YES	5256.84 (-105.20)	--	62.7%	32.8%
CL	EGFR BSA	Power	2	YES	5255.233 (-106.81)	--	62.5%	32.6%
CL	EGFR BSA	Exponent	2	NO	--	--		
CL	EGFR BSA	Hill	4 ^a	YES	5255.23 (-106.81)	5277.232 (-100.81)	62.4%	32.6%
V	WT	Linear	1	YES	5355.784 (-6.26)	--	66.3%	23.8%
V	WT	Allometric	1	YES	5370.212 (-8.17)	--	64.7%	17.4%
V	WT	Power	1	YES	5356.212 (-5.83)	--	66.4%	24.1%
V	WT	Exponent	1	YES	5355.752 (-6.29)	--	66.2%	23.8%
V	HT	Linear	1	YES	5361.798 (-0.25)	--	67.9%	29.6%
V	HT	Power	1	YES	5361.823 (-0.22)	--	67.9%	29.6%
V	HT	Exponent	1	YES	5361.787 (-0.26)	--	67.9%	29.6%
V	BSA	Linear	1	YES	5356.494 (-5.55)	--	66.6%	24.1%
V	BSA	Power	1	YES	5356.798 (-5.25)	--	66.6%	24.2%
V	BSA	Exponent	1	YES	5356.236 (-5.81)	--	66.5%	23.8%
V	AGE	Linear	1	YES	5352.470 (-9.58)	--	67.9%	35.1%
V	AGE	Piecewise	1	YES	5349.500 (-12.55)	--	68.0%	34.6%
V	AGE	Power	1	YES	5354.434 (-7.61)	--	67.9%	35.5%
V	AGE	Exponent	1	YES	5351.56 (-10.49)	--	67.9%	35.7%
V	SEX	Add Shift	1	YES	5361.850 (-0.20)	--	67.8%	30.0%
V	ICU	Add Shift	1	YES	5360.239 (-1.81)	--	68.6%	29.2%

Round 2 (Reference Model = Base + EGFR-CL)

REF	--	--	--	--	5226.141	5246.141	59.3%	32.2%
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CL	WT	Linear	1	YES	5198.150 (-27.99)	--	55.1%	30.8%
CL	WT	Allometric	0	YES	5197.500 (-28.64)	--	55.2%	30.8%
CL	WT	Power	1	YES	5197.500 (-28.64)	--	55.2%	30.8%
CL	WT	Exponent	1	YES	5200.707 (-25.43)	--	55.4%	30.9%
CL	HT	Linear	1	YES	5205.278 (-20.86)	--	56.7%	32.1%
CL	HT	Power	1	YES	5205.305 (-20.84)	--	56.7%	32.1%
CL	HT	Exponent	1	YES	5205.671 (-20.47)	--	56.7%	32.0%
CL	BSA	Linear	1	YES	5192.930 (-33.21)	--	54.6%	30.8%
CL	BSA	Power	1	YES	5193.748 (-32.39)	--	54.7%	30.8%
CL	BSA	Exponent	1	YES	5195.663 (-30.48)	--	54.8%	30.8%
CL	AGE	Linear	1	YES	5211.940 (-14.20)	--	58.7%	32.8%
CL	AGE	Piecewise	1	YES	5201.568 (-24.57)	--	58.1%	32.8%
CL	AGE	Power	1	YES	5218.856 (-7.29)	--	59.0%	32.6%
CL	AGE	Exponent	1	YES	5213.879 (-12.26)	--	58.8%	32.6%
CL	SEX	Add Shift	1	YES	5218.061 (-8.08)	--	58.1%	31.8%
CL	ICU	Add Shift	1	YES	5225.570 (-0.57)	--	59.3%	32.0%
V	WT	Linear	1	YES	5213.761 (-12.38)	--	57.3%	23.7%
V	WT	Allometric	1	YES	5223.192 (-2.95)	--	56.5%	19.4%
V	WT	Power	1	YES	5214.972 (-11.17)	--	57.5%	23.9%
V	WT	Exponent	1	YES	5213.233 (-12.91)	--	57.2%	23.4%
V	HT	Linear	1	YES	5223.916 (-2.22)	--	59.1%	29.7%

V	HT	Power	1	YES	5223.939 (-2.20)	--	59.1%	29.6%
V	HT	Exponent	1	YES	5223.683 (-2.46)	--	59.1%	29.4%
V	BSA	Linear	1	YES	5214.512 (-11.63)	--	57.7%	23.8%
V	BSA	Power	1	YES	5214.96 2(-11.18)	--	57.7%	23.6%
V	BSA	Exponent	1	YES	5213.357 (-12.78)	--	57.4%	23.0%
V	AGE	Linear	1	YES	5225.229 (-0.91)	--	59.4%	33.4%
V	AGE	Piecewise	1	YES	5222.415 (-3.73)	--	59.6%	34.6%
V	AGE	Power	1	YES	5225.893 (-0.25)	--	59.4%	32.8%
V	AGE	Exponent	1	YES	5225.133 (-1.01)	--	59.4%	33.4%
V	SEX	Add Shift	1	YES	5225.329 (-0.81)	--	59.1%	31.4%
V	ICU	Add Shift	1	YES	5221.674 (-4.47)	--	60.4%	30.6%

Round 3 (Reference Model: Base + EGFR-CL + BSA-CL)

REF	--	--	--	--	5192.930	5214.930	54.6%	30.8%
CL	AGE	Linear	1	YES	5180.400 (-12.53)	--	54.1%	31.2%
CL	AGE	Piecewise	1	YES	5171.469 (-21.46)	--	53.9%	31.2%
CL	AGE	Power	1	YES	5186.201 (-6.73)	--	54.4%	31.2%
CL	AGE	Exponent	1	YES	5181.897 (-11.03)	--	54.1%	31.2%
CL	SEX	Add Shift	1	YES	5191.640 (-1.29)	--	54.5%	30.7%
CL	ICU	Add Shift	1	YES	5192.854 (-0.08)	--	54.6%	30.7%
V	WT	Linear	1	YES	5132.698 (-60.23)	--	49.9%	18.1%
V	WT	Allometric	0	YES	5136.686 (-56.24)	--	50.6%	19.1%
V	WT	Power	1	YES	5132.700 (-60.23)	--	49.9%	18.1%

V	WT	Exponent	1	YES	5135.219 (-57.71)	--	49.9%	18.3%
V	HT	Linear	1	YES	5192.930 (-12.49)	--	54.1%	26.0%
V	HT	Power	1	YES	5179.586 (-13.34)	--	54.1%	25.6%
V	HT	Exponent	1	YES	5178.946 (-13.98)	--	54.1%	25.3%
V	BSA	Linear	1	YES	5132.882 (-60.05)	--	50.4%	17.8%
V	BSA	Power	1	YES	5131.150 (-61.78)	--	50.1%	17.5%
V	BSA	Exponent	1	YES	5131.023 (-61.91)	--	50.1%	17.4%
V	AGE	Linear	1	YES	5192.397 (-0.53)	--	54.7%	31.8%
V	AGE	Piecewise	1	YES	5190.518 (-2.41)	--	54.8%	32.9%
V	AGE	Power	1	YES	5192.803 (-0.13)	--	54.6%	31.3%
V	AGE	Exponent	1	YES	5192.350 (-0.58)	--	54.7%	31.9%
V	SEX	Add Shift	1	YES	5188.602 (-4.33)	--	54.4%	29.3%
V	ICU	Add Shift	1	YES	5188.872 (-4.06)	--	56.0%	29.3%

Round 4 (Reference Model: Base + EGFR-CL + BSA-CL + BSA-V)

REF	--	--	--	--	5131.023		50.1%	17.4%
CL	AGE	Linear	1	YES	5121.421 (-9.60)	--	49.9%	17.6%
CL	AGE	Piecewise	1	YES	5113.737 (-17.29)	--	49.7%	17.9%
CL	AGE	Power	1	YES	5125.759 (-5.26)	--	50.0%	17.5%
CL	AGE	Exponent	1	YES	5122.253 (-8.77)	--	49.9%	17.5%
CL	SEX	Add Shift	1	YES	5129.845 (-1.18)	--	50.0%	17.4%
CL	ICU	Add Shift	1	YES	5131.009 (-0.01)	--	50.1%	17.4%
V	AGE	Linear	1	YES	5126.817 (-4.206)	--	50.0%	17.9%
V	AGE	Piecewise	1	YES	5115.910 (-15.11)	--	49.7%	18.2%
V	AGE	Power	1	YES	5128.686 (-2.34)	--	50.1%	18.1%

V	AGE	Exponent	1	YES	5126.316 (-4.71)	--	50.0%	18.5%
V	SEX	Add Shift	1	YES	5131.019 (-0.004)	--	50.1%	17.4%
V	ICU	Add Shift	1	YES	5130.938 (-0.085)	--	49.9%	17.5%

Round 5 (Reference Model: Base + EGFR-CL + BSA-CL + BSA-V + AGE-CL)

CL	SEX	Linear	1	YES	5112.193 (-1.54)	--	49.6%	17.9%
CL	ICU	Linear	1	YES	5113.543 (-0.19)	--	49.7%	18.0%
V	AGE	Linear	1	YES	5113.333 (-0.40)	--	49.7%	17.9%
V	AGE	<i>Piecewise</i>	1	YES	5109.731 (-4.01)	--	49.5%	17.6%
V	AGE	Power	1	YES	5113.595 (-0.142)	--	49.7%	18.0%
V	AGE	Exponent	1	YES	5113.126 (-0.036)	--	49.7%	18.1%
V	SEX	Linear	1	YES	5113.701 (-0.036)	--	49.7%	17.9%
V	ICU	Linear	1	YES	5113.668 (-0.069)	--	49.6%	17.9%

Round 6 (Reference Model: Base + EGFR-CL + BSA-CL + BSA-V + AGE-CL + AGE-V)

CL	SEX	Add Shift	1	YES	5108.257 (-1.47)	--	49.4%	17.5%
CL	ICU	Add Shift	1	YES	5109.623 (-0.11)	--	49.5%	17.6%
V	SEX	Add Shift	1	NO	5109.728 (-0.003)	--	49.5%	17.6%
V	ICU	Add Shift	1	YES	5109.592 (-0.139)	--	49.2%	17.7%

Bold italic text indicates the best covariate model from the forward selection round. Covariates will be retained in the model until additional covariates no longer lead to a decrease in the OFV greater than the corresponding critical value from the chi-square distribution at the indicated DF and an alpha of 0.05. These values are 3.84 and 5.99 for 1 and 2 DF, respectively.

^aIndicates non-nested model. Comparison to reference model should be made by AIC

Table S5: Backward Elimination of Covariates

PAR	COV	Functional Form	DF	MIN, ROUND, & COVAR Successful	OFV (Δ OFV)	AIC (Δ AIC)	BSV CL	BSV V
Round 1 (Reference Model: Base + EGFR-CL + BSA-CL + BSA-V + AGE-CL + AGE-V)								
REF	--	--	--	--	5109.731	5137.731	49.5%	17.6%
CL	EGFR	Power	2	YES	5216.239 (+106.51)	5240.239 (+102.51)	54.4%	16.5%
CL	EGFR	Power = 1	1	YES	5110.094 (+0.36)	5136.094 (-1.64)	49.6%	17.7%
CL	BSA	Linear	1	YES	5189.073 (+79.34)	5215.073 (+77.34)	56.5%	23.7%
V	BSA	Exponent	1	YES	5171.027 (+61.30)	5197.027 (+59.30)	53.9%	30.8%
CL	AGE	Piecewise	1	YES	5115.910 (+6.18)	5141.90 (+4.18)	49.5%	17.6%
V	AGE	Piecewise	1	YES	5113.737 (+4.01)	5139.737 (+2.01)	49.5%	17.6%
Round 2 (Reference Model: Base + EGFR-CL + BSA-CL + BSA-V + AGE-CL + AGE-V)								
REF	--	--	--	--	5110.094	5136.094	49.6%	17.7%
CL	EGFR	Linear	1	YES	5216.239 (+106.14)	5240.239 (+104.14)	54.5%	16.5%
CL	BSA	Linear	1	YES	5191.512 (+81.42)	5215.512 (+79.42)	57.1%	24.6%
V	BSA	Exponent	1	YES	5171.149 (+61.06)	5195.149 (+59.06)	53.9%	30.9%
CL	AGE	Piecewise	1	YES	5117.040 (+6.95)	5141.040 (+4.95)	49.9%	18.4%
V	AGE	Piecewise	1	YES	5114.238 (+4.14)	5138.238 (+2.14)	49.9%	18.0%
Round 3 (Reference Model: Base + EGFR-CL + BSA-CL + BSA-V + AGE-CL)								
REF	--	--	--	--	5114.238	5138.238	49.9%	18.0%
CL	EGFR	Power	1	YES	5218.454 (+104.22)	5240.454 (+102.22)	54.7%	16.9%
CL	BSA	Linear	1	YES	5191.521 (+77.28)	5213.521 (+75.28)	57.1%	24.7%
V	BSA	Exponent	1	YES	5171.551 (+57.31)	5193.551 (+55.31)	54.0%	31.4%

CL	AGE	Piecewise	1	YES	5133.825 (+19.59)	5155.825 (+17.59)	50.4%	17.6%
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Bold italic text indicates the covariates meeting criteria for backward elimination. Covariates will be eliminated if the OFV increases by less than the corresponding critical value from the chi-square distribution at the corresponding DF and an alpha of 0.001. These values are 10.83 and 13.82 for 1 and 2 DF, respectively.

Table S6: Final Covariate Structured Model Parameter Estimates

Parameter	Estimate	Relative Standard Error (%)	Shrinkage (%)
Fixed Effects			
TVCLNR (θ_1) [L/hr/1.89 m ²]	3.43	8%	
BSA on CL (θ_5)	3.49	10%	
AGE on CL (θ_7)	0.0242	27%	
TVCLR (θ_4) [L/hr/80 mL/min]	1.77	11%	
TVV (θ_2) [L]	42.90	3%	
BSA on V (θ_6)	0.901	11%	
TVKA (θ_3) [hr ⁻¹]	1.40	17%	
Between-subject Variability (BSV)^a			
BSV CL (ω_1) [%CV]	49.9%	4%	15%
BSV V (ω_2) [%CV]	17.8%	16%	45%
Correlation BSV CL-V ^b	0.679		
Residual Variability (RV)			
Additive Error (θ_9) [mg/L]	1.43	19%	
Proportional Error (θ_{10}) [%CV]	27.1%	6%	

^a BSV calculated as $\sqrt{e^{\omega^2} - 1}$

^b Expressed as correlation coefficient (r)

CL covariate structure:

$$CL \left(\frac{L}{hr} \right) = CLNR + CLR$$

$$CLNR \left(\frac{L}{hr} \right) = TVCLNR + \theta_5 \times (BSA - 1.89) - \theta_7 \times (AGE - 40) * AGEIND ; \\ AGEIND is 1 if AGE > 40 and 0 if AGE \leq 40$$

$$CLR \left(\frac{L}{hr} \right) = TVCLR * \left(\frac{EGFR}{80} \right)$$

V covariate structure:

$$V(L) = TVV * e^{\theta_6 \times (BSA - 1.89)}$$

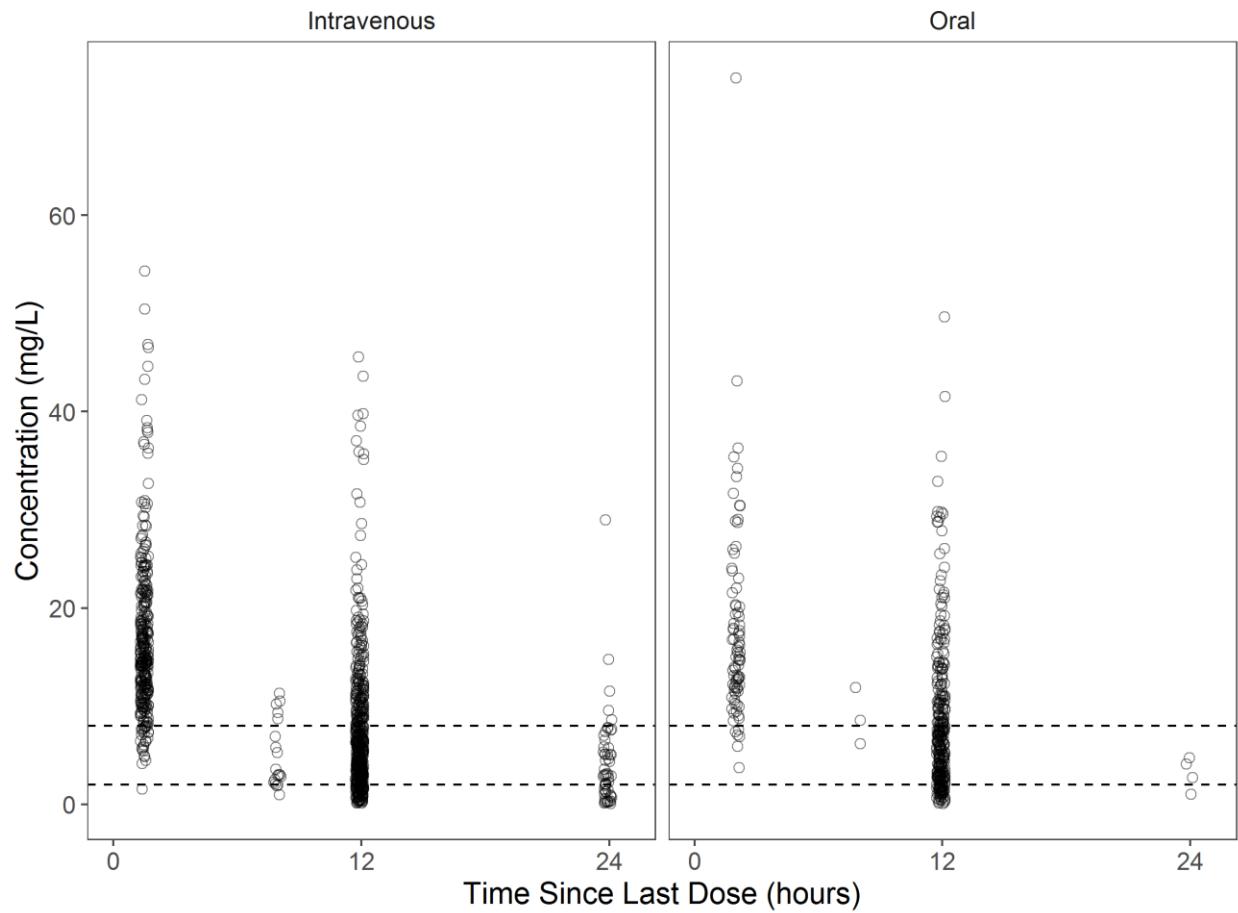


Figure S1: Concentration versus Time Since Last Dose Stratified by Route of Administration.

Dashed lines represent the therapeutic range of 2 – 8 mg/L for trough concentrations.

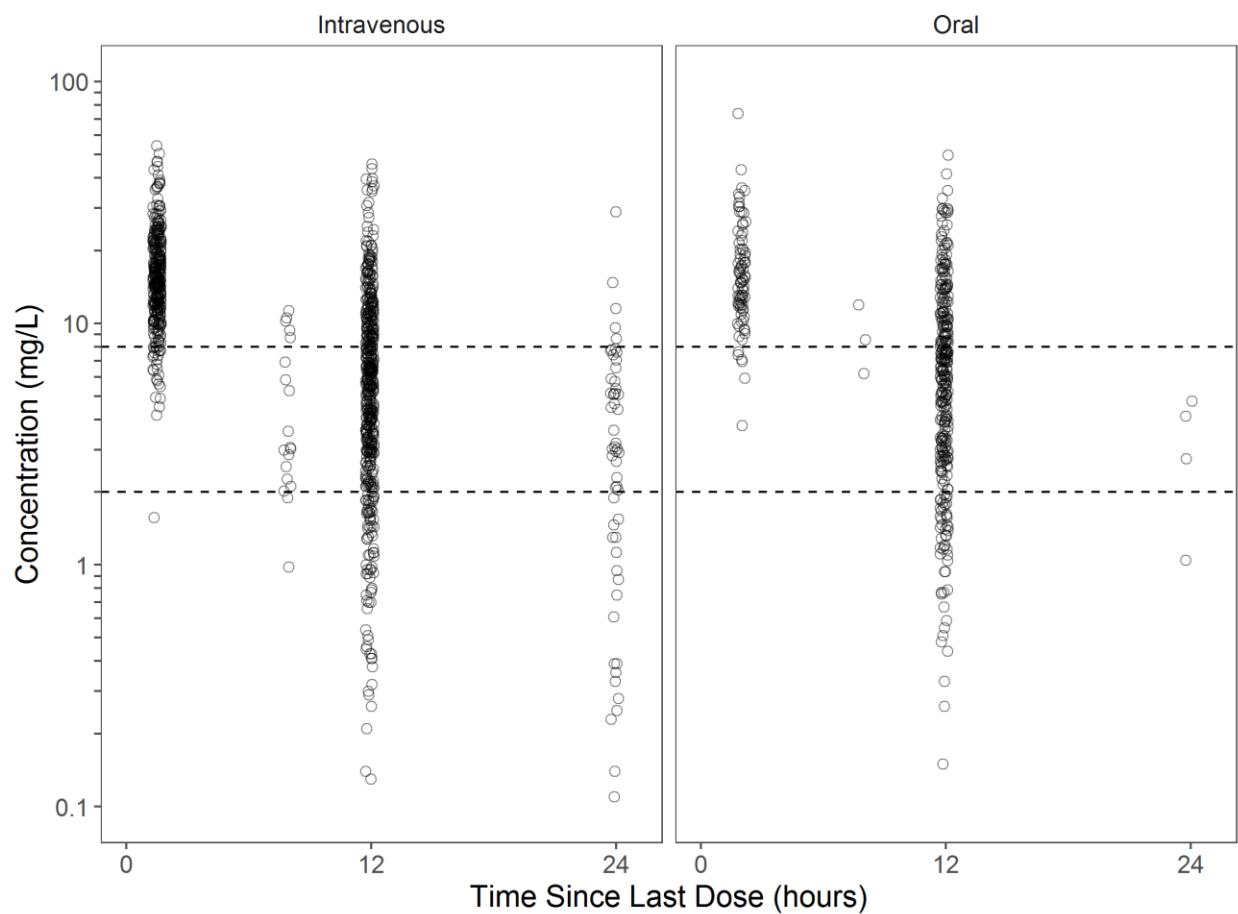


Figure S2: Concentration versus Time Since Last Dose Stratified by Route of Administration on a Semi-log Scale. Dashed lines represent the therapeutic range of 2 – 8 mg/L for trough concentrations.

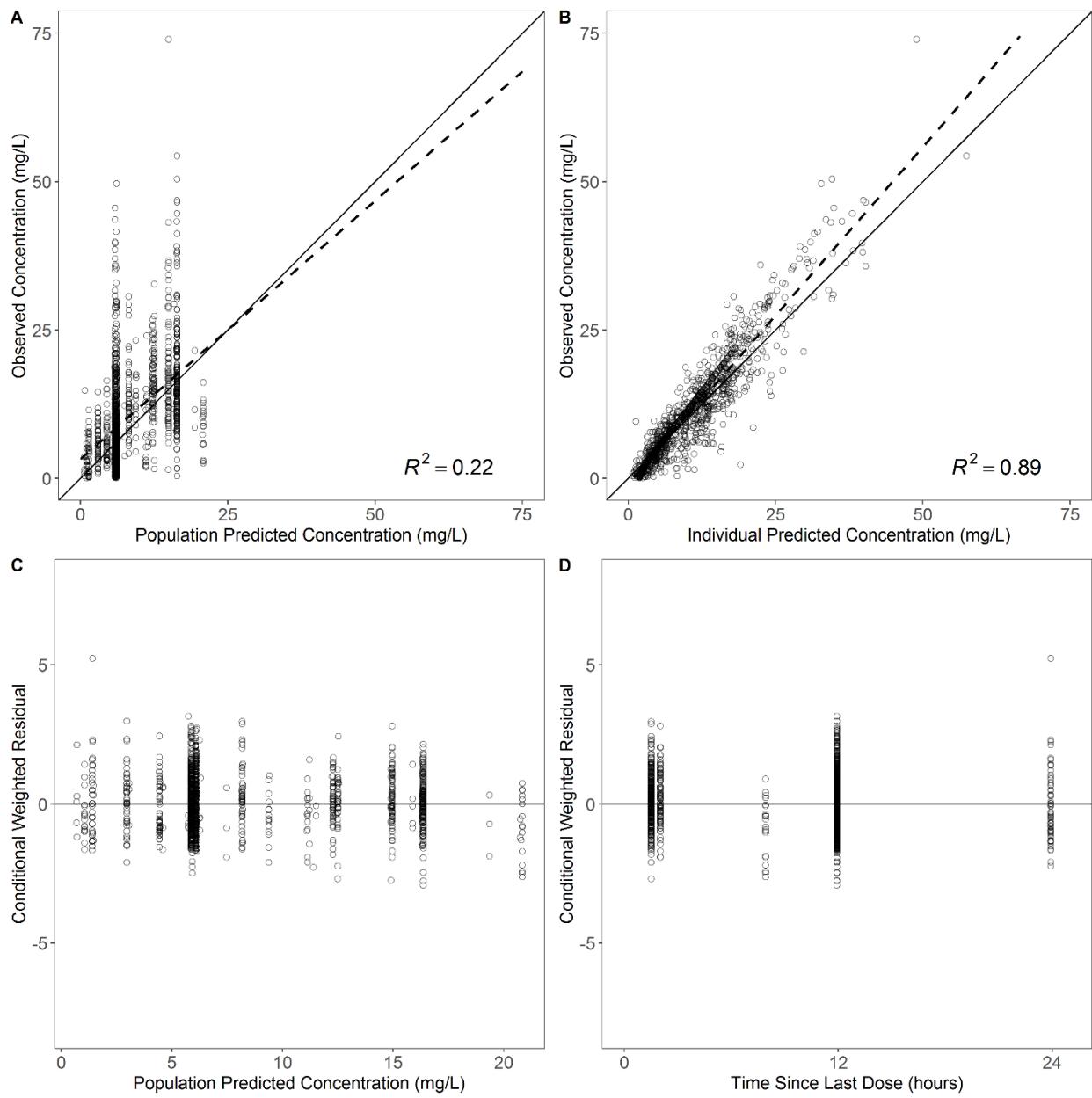


Figure S3: Population Prediction Diagnostic Plots of the Base Model. Panels A and B depict plots of observed linezolid concentrations versus population (A) and individual (B) model-predicted concentrations, respectively. Panels C and D depict plots of conditional weighted residuals versus population predicted concentrations and time since last dose, respectively. Solid lines indicate the y-axis value is equal to unity (Panels A and B) or null (Panels C and D) while dashed lines represent the linear (Panels A and B) fits of the data.

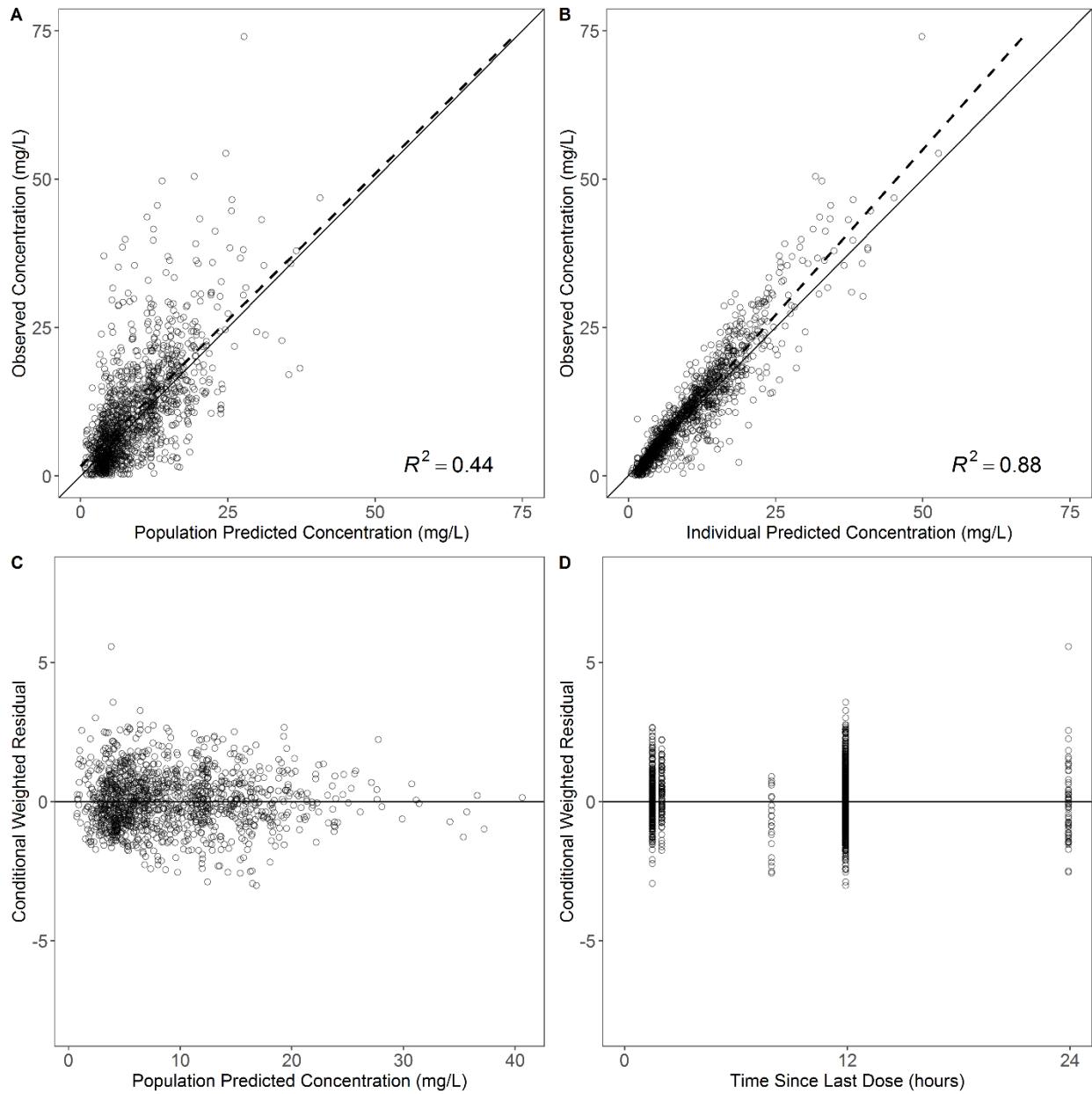


Figure S4: Population Prediction Diagnostic Plots of the Final Covariate-structured Model.

Panels A and B depict plots of observed linezolid concentrations versus population (A) and individual (B) model-predicted concentrations, respectively. Panels C and D depict plots of conditional weighted residuals versus population predicted concentrations and time since last dose, respectively. Solid lines indicate the y-axis value is equal to unity (Panels A and B) or null (Panels C and D) while dashed lines represent the linear (Panels A and B) fits of the data.

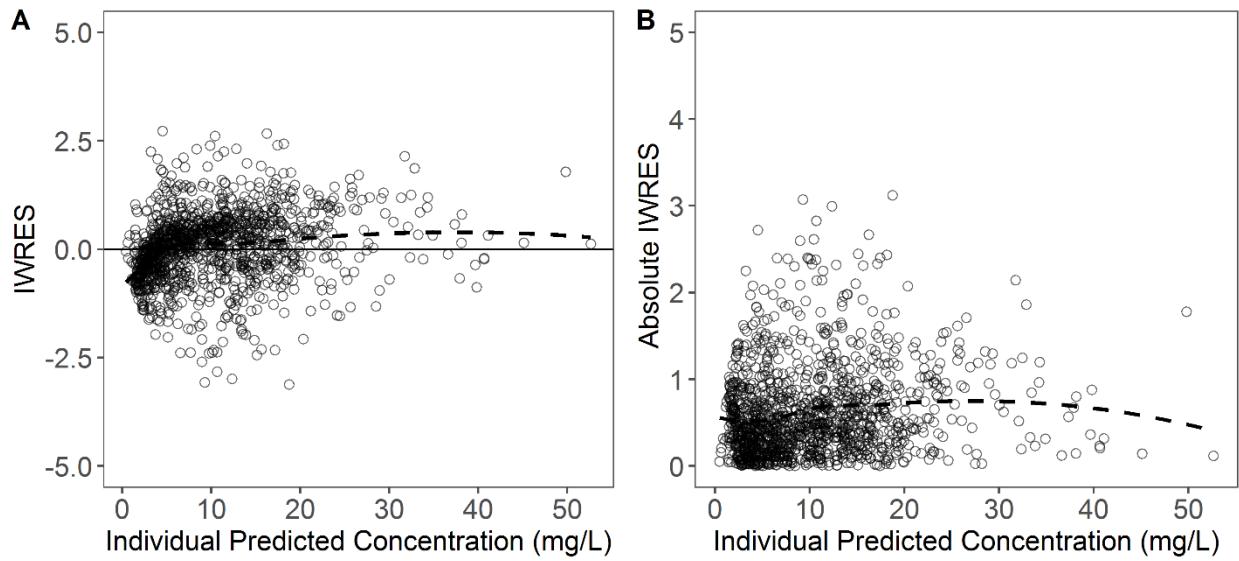


Figure S5: Individual Prediction Diagnostic Plots of the Final Covariate-structured Model.

Panels A and B depict plots of individual weight residuals (IWRES) and the absolute value of IWRES, respectively, versus individual predicted concentrations. Dashed lines represent the LOESS fits of the data.

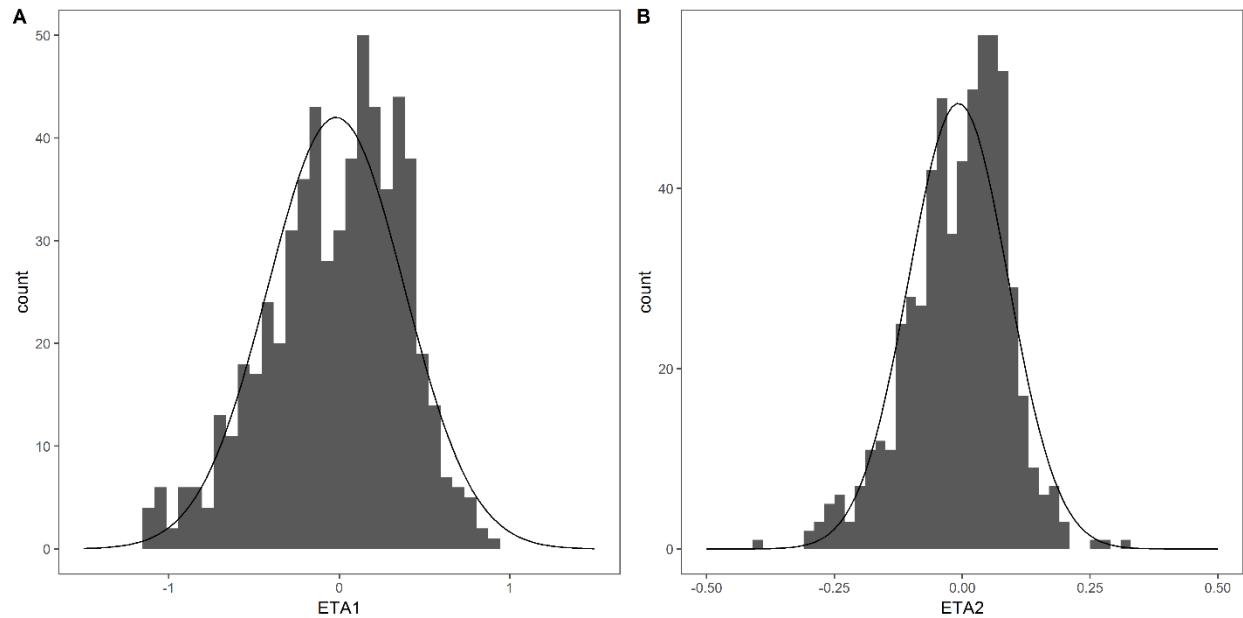


Figure S6: Histograms of Individual ETA Estimates from the Final Covariate-structured Model.

Panels A and B depict individual estimates of ETA1 (CL) and ETA2 (V) with an overlaid normal distribution.

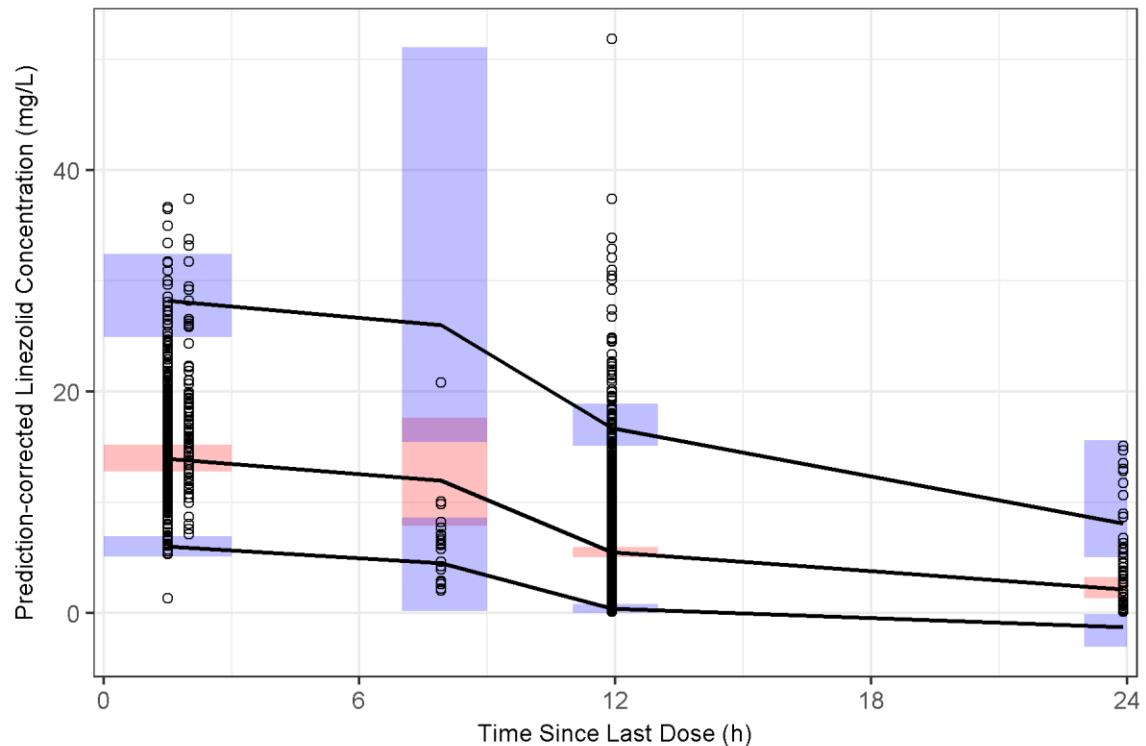


Figure S7: Prediction-corrected Visual Predictive Check of the final Covariate-structured Population Pharmacokinetic Model. Solid lines indicate the 5th, 50th, and 95th percentiles of the model predicted linezolid concentrations. Red shaded areas indicate the 95% confidence interval of the median prediction while blue shaded areas indicate the 95% confidence intervals of the 5th and 95th predicted concentrations. Open circle depict the observed data.